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Final Report

THE METABOLISM OF CONNECTIVE TISSUE

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1. Research Objectives:

- a) To obtain a knowledge of the chemical structure and physical properties of connective tissue constituents such as hyaluronic acid complexes.
- b) To obtain information concerning the formation and destruction of collagen as affected by vitamins, and hormones.
- c) To elucidate the mechanism of formation of collagen and inquire about the role of ascorbic acid and hyaluronate in this process.

2. Evaluation of approach to the problem:

Biochemical techniques have been applied to problems which for the most part have been studied by histologic methods. The results already obtained and some of the problems opened up and being investigated at present attest to the value of the approach.

3. Research progress accomplishments and status:

- a) A method has been developed for the isolation of hyaluronate from synovial fluid and connective tissue which does not result in its depolymerisation. This method is relatively simple and permits accumulation of large amounts of native hyaluronate. With these it should be possible to decide in what form (free or as protein-complex) hyaluronate exists in nature and to study the physical properties of the material.
- b) It has been found that neither organ collagen nor repair collagen requires ascorbic acid once it has been formed; nor is the amino acid turnover specifically affected by vitamin C.

A technique for producing sufficient new connective tissue of uniform maturity for chemical analyses has been developed. Making use of this method it has been possible to demonstrate that vitamin C is required in the formation of collagen and that vitamin A is not. Estrogens, desoxycorticosterone and adrenalectomy stimulate, cortisone inhibits and progesterone, testosterone or age have no effect on collagen formation in this new connective tissue.

- c) The evidence obtained in our studies of collagen formation suggest that in the absence of ascorbic acid a collagen precursor is formed which contains less hydroxyproline than collagen. In the absence of ascorbic acid hyaluronate is formed in excess and disappears when the ascorbic acid deficiency is repaired.

5. Personnel:

Professional: Wm. v. B. Robertson, responsible investigator
May 1 1949 - April 30, 1953 - $\frac{1}{2}$ time

Research assistants (technician):

E. Tuttle - June 15, 1949 - Oct. 15, 1950
P. Peyser - June 15, 1949 - Sept. 15, 1949
E. C. Sanborn - Sept. 15, 1950 - Aug. 31, 1951
(Mar. 1, 1952 - April 30, 1952 - $\frac{1}{2}$ time)
B. Schwartz - June 18, 1951 - Sept. 15, 1952
H. Hinds - Sept. 1, 1952 - April 31, 1953

Student Assistants:

Herbert Dickerman - June 15 - Sept. 10, 1949
June 15 - Sept. 10, 1950
Arthur Kunin - June 15 - Sept. 10, 1949
June 15 - Sept. 10, 1950
Murdo MacDonald - June 15 - Sept. 1, 1949
David Maxhem - June 15 - Sept. 1, 1950
June 11 - Sept. 1, 1951
Valmore Cross - June 11 - Sept. 1, 1951
Manfred Goldwein - June 18 - Sept. 1, 1951
June 15 - Sept. 1, 1952

6. Publications:

Reports: Quarterly Progress Summary - May 1 - Aug. 31, 1949
" " " Oct. 1 - Dec. 31, 1949
Semiannual Progress - Jan. 1 - June 30, 1950
" " Jan. 1 - June 30, 1951
Jan. 1 - June 30, 1952
Annual Progress - Jan 1 - Dec. 31, 1950
Jan 1 - Dec. 31, 1951
Jan 1 - Dec. 31, 1952

Published manuscripts:

Concentration of Collagen in Guinea Pig Tissues in Acute and Prolonged Scurvy - William van B. Robertson; J. Biol. Chem. 187:673, 1950. Submitted June 29, 1950.

The Metabolism of Connective Tissue: Absence of Alkaline Phosphatase in Collagen Fibres During Formation. - W. van B. Robertson, F. W. Dunihue and A. B. Novikoff. Brit. J. Exp. Path. 31:545, 1950. Submitted June 17, 1950.

The Effect of Ascorbic Acid Deficiency on the Collagen Concentration of Newly Induced Fibrous Tissue - Wm. van B. Robertson; J. Biol. Chem. 196:403, 1952. Submitted Dec. 27, 1951.

Influence of Ascorbic Acid on N-15 Incorporation into Collagen in Vivo - Wm. van B. Robertson - J. Biol. Chem. 197:495, 1952. Submitted Mar. 3, 1952.

Ascorbic Acid and the Formation of Collagen - Wm. van B. Robertson and Barry Schwartz - J. Biol. Chem. 201:689, 1953. Submitted Sept. 26, 1952.

Abstracts: Effects of Ascorbic Acid on the Connective Tissue
Reaction Induced in Guinea Pigs by Estrogen - Wm. V. B. Robertson,-
F. W. Dunihue, E. L. Sanborn - J. Clin. Endocr. 11:784, 1951

Collagen Formation in Vitamin A - Deficient Rats - Wm. V. B. Robert-
son, V. Cross - Fed. Proc. 1952.